UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,166	11/17/2000	Douglas A. Treco	10278-014001	6951

26161 7590 06/03/2004

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
JIANG, DONG	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/716,166	TRECO ET AL.	
	Examiner	Art Unit	
	Dong Jiang	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-14,17,19,21-46 and 83-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-14,17,19,21-46 and 83-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's amendment filed on 05 March 2004 is acknowledged and entered. Following the amendment, claims 15, 16 and 47-82 are canceled, and claims 1, 14, 19, 27, 39 and 83 are amended.

Currently, claims 1-6, 8-14, 17, 19, 21-46 and 83-93 are pending, and under consideration.

Withdrawal of Objections and Rejections:

All objections and rejections of claims 15 and 47-52 are moot as the applicant has canceled the claims.

The objection of claims 32 and 36 as being dependent upon a canceled claim is withdrawn in view of applicant's amendment.

The rejection of claims 1-6, 8-14, 17, 19, 21-46 and 83 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendment.

The rejection for lack of written description of claim 83 under 35 U.S.C. 112, first paragraph is withdrawn in view of applicant's amendment.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 and 8-13 remain rejected, and claims 90 and 91 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19), in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55, provided by applicants), Habener et al. (US 5,118,666), Suzuki et al. (US 5,891,671), and Patel et al. (CIBA Foundation Sumposium, 1995, 190: 26-50), for the reasons of record set forth in the last Office Action, paper No. 14, mailed on 09 September 2003, at pages 9-11.

Note: applicants point out that the prior art rejection of claims 5, 9, 11 and 13 under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19), and further in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55, provided by applicants), Habener et al. (US 5,118,666), Suzuki et al. (US 5,891,671), and Patel et al. (CIBA Foundation Symposium, 1995, 190: 26-50), was indicated to be withdrawn in the beginning of the last Office Action, and then rejected later over the same references. Upon reviewing the last Office Action, the Examiner confirms that the prior art rejection of claims 5, 9, 11 and 13 should not have been withdrawn.

Applicants argument filed on 05 March 2004 has been fully considered, but is not deemed persuasive for reasons below.

At pages 12-13 of the response, the applicant argues that the cited references lack the requisite specific motivation and reasonable expectation of success to combine the references to arrive at the specific claimed constructs, that neither Sevarino nor Stoller's results are predictive of whether one could successfully express any heterologous non-somatostatin small peptide as claimed, and that the fact that producing GLP-1 might be generally desirable does not provide a motivation to make any one specific method or construct for producing it. Applicants further argue that the Examiner appears to have merely plucked limitations from numerous prior art references and pieced them together using the claims as a template, which is impermissible by the Federal Circuit. This argument is not persuasive for the following reasons. With respect to motivation, besides the therapeutic reasons for making GLP-1 taught by Habener, Suzuki teaches

that it is desirable in the art to utilize the expression of a chimeric protein for a number of peptide production including GLP-1 (column 5, lines 13-22), that enzymatic cleavage such as furin can be used for separating a target peptide (column 1, lines 15-18), and that it is expected that the peptide hormone is not damaged and the processing enzyme is applicable to a wide variety of peptides, therefore, the development of such production methods has been desired in the art (column 1, lines 36-49), and Sevarino and Stoller teach that the pro-region of preprosomatostatin can be used for targeting a heterologous peptide to regulated secretory pathway. The teachings of Suzuki, Sevarino and Stoller provide strong motivation to make the construct as claimed because it would allow the target peptide to be secreted, which would greatly facilitate the purification process.

With respect to reasonable expectation of success, and the argument that neither Sevarino nor Stoller's results are predictive of whether one could successfully express any heterologous non-somatostatin small peptide as claimed, the requirement for a reasonable expectation of success does *not* rest on *a complete certainty* of success. A prior art reference only needs to provide an indication of a *reasonable expectation* of success. In the instant case, Sevarino and Stoller have demonstrated successful expression of two different heterologous peptides by using fusing pro-region of prosomatostatin with the target peptide. Although Sevarino target peptide is the C- terminal portion of the anglerfish preprosomatostatin-2, it is a small heterologous peptide, indicating that the pro-region of the preprosomatostatin is able to direct the expression and secretion of a small heterologous peptide. Further, Stoller's target peptide is a heterologous polypeptide α-globin, not a "small" peptide. The combined results by Sevarino and Stoller strongly indicate that the expression system comprising prepro-region of a preprosomatostatin can be suitable for a broad range of peptides with different sizes. One of ordinary skill in the art would consider that two successful examples of different heterologous peptides are sufficient to provide an indication of a *reasonable expectation* of success for the expression of other heterologous peptides.

With respect to the argument that the Examiner appears to have merely plucked limitations from numerous prior art references and pieced them together using the claims as a template, which indicates that the examiner's conclusion of obviousness is based upon

improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

With respect to claims 90 and 91, although the prior art references do not teach a variant of the pro-region of somatostatin, making and testing a functional variant were well within the skill of the art, and was widely practiced in the field at the time the present invention was made.

Claims 14, 17, 19, 21-35, 37-46, and 83-89 remain rejected, and claims 92 and 93 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19), and in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55, provided by applicants), Habener et al. (US 5,118,666), Suzuki et al. (US 5,891,671), and Patel et al. (CIBA Foundation Sumposium, 1995, 190: 26-50), as applied to claims 1-6 and 8-13 above, and further in view of Warren et al. (Cell, 1984, 39(3 Pt2): 547-55), and Selden et al., US 6,531,124 B1, for the reasons of record set forth in the last Office Action, paper No. 14, mailed on 09 September 2003, at pages 11-13.

Applicants argument filed on 05 March 2004 has been fully considered, but is not deemed persuasive for reasons below.

At pages 14-15 of the response, the applicant argues that none of the references, alone or in any combination, provide a motivation or suggestion to link the pro-region of somatostatin to a non-somatostatin small peptide in a non-endocrine cell, as claimed, and that nothing in Selden suggest that GLP-1 can be produced in a non-endocrine cell by linking GLP-1 to the somatostatin pro-region. This argument is not persuasive for the following reasons. As the issues of the motivation and reasonable expectation of success regarding the construct are addressed above, the issue to discuss herein is focused on the motivation to choose the cell type as claimed.

In response to applicant's argument that nothing in Selden suggests that GLP-1 can be produced in a non-endocrine cell by linking GLP-1 to the somatostatin pro-region, it is against the references individually. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, if Selden had suggested that GLP-1 can be produced in a non-endocrine cell by linking GLP-1 to the somatostatin pro-region, the claims would have been rejected under 35 U.S.C. 102 as being anticipated by the reference. Further, even though Selden does not teach that GLP-1 can be produced in a non-endocrine cell by linking GLP-1 to the somatostatin pro-region, the suggestion or motivation to do so can be found in the combined references, which teach that it is obvious to make the construct as claimed (discussed above), and the somatostatin pro-region expression system works in non-endocrine cells (taught by Warren and Patel), which greatly broaden the range of cells that can be used for expressing peptides. The point to learn from Selden is that small peptides such as GLP-1 can be expressed in either primary or secondary cells, which are useful for gene therapy, and provides strong motivation for choosing these cells. Warren and Patel's results of using the somatostatin pro-region expression system in non-endocrine cells further provides an indication of reasonable expectation of success.

Applicants further argue, at page 16 of the response, that Warren and Patel's results teaches away from the claimed cells because of a relative low level of secretion and inefficient cleavage in non-endocrine cells. This argument is not persuasive because Warren further states that "however, in the absence of quantitative data we cannot accurately compare either the levels of proteolytic processing or secretion of the two hormones in these different cell types (page 553, the right column). As such, one of ordinary skill in the art would not accept the argument as an evidence that the reference teaches away from the claimed cells. Applicants further argue that

the Patel reference has a later publication date than the Warren reference, and is therefore more representative of the state of the art. In response to applicant's argument based upon the age of the references, contentions that the reference patents are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977).

With respect to claims 92 and 93, although the prior art references do not teach a variant of the pro-region of somatostatin, making and testing a functional variant were well within the skill of the art, and was widely practiced in the field at the time the present invention was made.

Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sevarino et al. (Cell, 1989, 57(1): 11-19), and in view of Stoller et al. (J. Cell Biol., 1989, 108: 1647-55), and Warren et al. (Cell, 1984, 39(3 Pt2): 547-55), as applied to claims 14, 17, 19, 21-35, 37-46 and 83-89 above, and further in view of Nagai et al., US 6,010,883.

The teachings of Sevarino, Stoller, and Warren are reviewed in the previous Office Actions. None of the references teaches a cleavage site which is a blood coagulation factor cleavage site.

Nagai teaches *improved* cleavage linkers for use in the construction of recombinant DNAs which encode for fusion proteins, as these cleavage sites are rarely found in other proteins and thus they will be suitable for use in the cleavage of a very wide range of recombinant fusion proteins, and cleavage by the enzyme at these sites is not dependent upon overall three dimensional structure as may be the case with other specific cleavage sequences (column 2, lines 44-55). Nagai's improved cleavage linkers include a cleavage site by blood coagulation factor Xa. Additionally, Nagai teaches the desired proteins or peptides to be expressed in this system, such as an enzyme, a serum protein, or *a peptide hormone* (Claim 14). Further, Nagai teaches a fusion product comprising the sequences encoding the linker cleaved by blood coagulation factor Xa and the desired protein or peptide, an expression vector comprising the fusion product, and a host cell thereof (claims 1, 8 and 16, for example).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to make a host cell as described in the claim transfected with the nucleic acid construct encoding a fusion protein comprising a signal peptide, a pro-region of a somatostatin, a cleavage site, and a desired protein as taught by Sevarino, Stoller, Warren, and Nagai for expressing a small peptide such as a peptide hormone, wherein the cleavage site is a blood coagulation factor cleavage site as taught by Nagai. The person of ordinary skill in the art would have been motivated to use a blood coagulation factor cleavage site because of the advantages taught by Nagai (see above), and reasonably would have expected success because Nagai has demonstrated successful cleavage of fusion proteins comprising such a cleavage site, and production of a foreign gene product in native form (Example 3, for example).

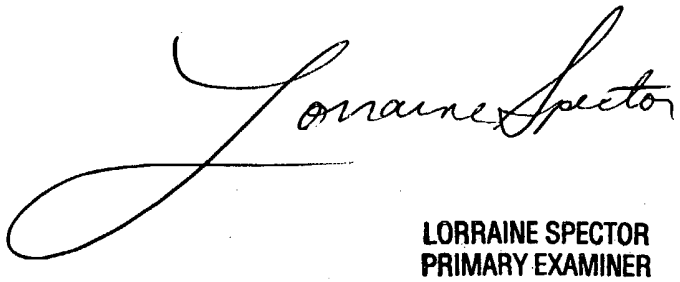
Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.



LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646
5/25/04